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PATRICIA GRANAHAN
HAMILTON, BROOK, SMITH & REYNOLDS
TWO MILITIA DRIVE
LEXINGTON MA 02173

| EXAMINER | |
|---|---|
| NGUYEN, D | |
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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Paper No. 45

Application Number: 08/187,879
Filing Date: January 27, 1994
Appellant(s): Robinson *et al.*

Elizabeth W. Mata
For Appellant

**EXAMINER'S ANSWER**

This is in response to Appellant's Brief on appeal filed March 5, 2001

*(1) Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

*(2) Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

*(3) Status of Claims*

The statement of the status of the claims contained in the Brief is not entirely correct with respect to claims 62-64, 68-70, 74 and 78-80. Claims 62-64, 68-70, 74 and 78-80 are not the subject of this appeal because the claims were already indicated by the examiner to applicants on May 22, 20001 as being allowable. However, Appellants instructed attorney Elizabeth Mata to telephone the examiner on June 1, 2001 to indicate that the proposed claims including the composition claims, the plasmid claims and proposed method claims (which enabling claimed methods are indicated on pages 7 and 8, and pages 25 and 26 of the examiner's answer) are not acceptable to Appellants.

*(4) Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

*(5) Summary of Invention*

The summary of invention contained in the Brief is substantially correct.

*(6) Issues*

The appellant's statement of the issues in the Brief is noted but not accurate. The changes are as follows: The issues in the instant case are whether the claims on appeal are enabled by the specification as of the effective filing date. The issue can be divided into groups (a)(i) and (a)(ii):

(a) With respect to claims 44-~~46~~ 50,51 and 82-89, the issue is whether the claimed invention is enabled for:

(i) A method of immunizing any SIV infectious mammal including humans against a simian immunodeficiency virus (SIV) comprising administering to the mammal a DNA transcription unit comprising a DNA encoding an antigen of said SIV by any administration route, whereby the mammal is protected from any disease by said SIV;

(ii) A method of immunizing any HIV infectious mammal including humans against a human immunodeficiency virus (HIV) comprising administering to the mammal a DNA transcription unit comprising a DNA encoding an antigen of said HIV by any administration route, whereby the mammal is protected from any disease by said HIV.

Note that with respect to claims 62-64, 68-70, 74 and 78-80, the claims were already indicated by the examiner to applicants on May 22, 20001 as being allowable, however, Appellants instructed attorney Elizabeth Mata to telephone the examiner on June 1, 2001 to indicate that the proposed claims including the composition claims, the plasmid claims and proposed method claims (which enabling claimed methods are indicated on page 8, and pages 26 and 27 of the examiner's answer) are not acceptable to Appellants.

In view of the entire prosecution history, *e.g.*, the nature of the invention, *e.g.*, DNA vaccine so as to generate any protective responses against any SIV or HIV infection in any mammal including a human, the state of the prior art, applicant's responses including the

Robinson Declaration (dated March 1, 1996, paper No. 15) and the Lu Declaration dated April 14, 2000, the examiner called applicants on Feb. 26, 2001 and May 22, 2001 to propose to applicants that the composition claims are allowable, and that if all claimed methods are amended to claim only a method of reducing SIV infected cells (group (a)(i)) or HIV infected cells (group (a)(ii)) in a mammal, wherein the method comprises the use of specifically named plasmid vector and method steps as shown by factual evidence in the 1.132 Declaration of Dr. Robinson (dated March 1, 1996, paper No. 15) which is the only Declaration that has factual evidence relevant to the claimed invention as finally amended on January 29, 2001 (paper No. 41), the amended claimed methods are in condition for allowance. However, during the last week of February, 2001, and on June 1, 2001 Appellant's representative, Attorney Elizabeth Mata, indicated to the examiner that the proposed amendment is not acceptable and that Appellants intend to pursue the appeal by filing the brief of appeal to properly address the issues of record.

As a result, the overall issues with respect to the groupings and the entire prosecution at the time the brief was file is:

- Whether the examiner erred in stating that the claims were not enabled in breadth and should be limited to only methods of reducing HIV or SIV infected cells in a mammal wherein the method comprises multiple administrations that comprises a gene gun administration of the constructs to the skin of a mammal as shown in the Robinson Declaration (Paper No: 15).

- Whether the examiner erred in stating since the state of the art of DNA vaccine or HIV or SIV remains reasonably unpredictable, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of a claim, particularly since it is apparent from the art of record that HIV antigens are all variable in their biological effects, that routes of administration in any DNA vaccine application are not equivalent or reasonable correlated with one another, that reduction of HIV or SIV infected cells are not the same as any protective response, *e.g.*, partial or complete protective response against a future infection of HIV or SIV, that an SIV model is not the same as an HIV model and they are not interchangeable, and that a showing of a temporary reduction of SIV infected cells in an animal model while the CD4 counts subsequently is not affected statistically and therapeutically is not same as claiming any SIV vaccine or HIV vaccine of any antigen expressing DNA that must exhibit the full breadth of "protective responses" as intended by the as-filed application.

*(7) Grouping of Claims*

Appellant's brief includes a statement that claims 44-46, 50, 51 and 81-89 stand or fall together, and that claims 62-64, 68-70, 74 and 78-80 stand or fall together. However, the statement is not accurate in view of the examiner's acknowledgement of a reasonable enablement

of the specifically named compositions and plasmids as claimed, and of the allowability of the composition and plasmid claims. As a result, there is only one grouping of claims: Claims 44-46, 50, 51 and 81-89 stand or fall together.

***(8) Claims Appealed***

The copy of the appealed claims contained in the Appendix to the Brief is correct. However, due to the examiner's acknowledgment of the allowability of the composition and plasmid claims, *e.g.*, claims 62-64, 68-70, 74 and 78-80, claims appealed presently are only claims 44-46, 50, 51 and 81-89.

***(9) References of Record***

The following is a listing of the art of record relied upon in the rejection of claims under appeal:

Haynes (Science, 260, pp. 1279-1286, 1993);

Tang *et al.* (Nature, Vol. 356, Vol. 356, pp. 152-154, 1992);

Hoffenbach *et al.* (J. of Immunology, 142, 2, pp. 452-462, 1989);

Butini *et al.* (J. or Cellular Biochemistry, Suppl. 18B:147, abstract J306, 1994);

Glasser (Genetic Engineering News, Biotech Firms Shifts Focus Toward Therapeutic HIV vaccine Development, 1996);

Rekosh *et al.* (PNAS, vol. 85, pp. 334-338, 1988);

Weiss (The Washington Post, Genetic Vaccine Keeps Chimps Protected Against AIDS Virus, page A2, 4/30/1997);

Cohen and Fauci (JAMA, Vol. 280, Vol. 280, No. 1: 87-88, 1998);

Kuby (Immunology, W.H. Freeman and Company, New York, 1992);

Gilboa and Smith (TIG, 1994, pages 141-142, paragraph bridging pages 141-142);

Johnson *et al.* (Intern. Rev. Immunol. Vol. 8, pp. 55-63, 1992).

*(10) New Prior Art*

No new prior art is relied upon by the examiner in the rejection of claims under appeal.

*(11) Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-46, 50, 51, and 81-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification only provides a reasonable enablement for claims directed to:

(I) A method of reducing SIV infected cells in a mammal, the method comprising administering to said mammal multiple administrations of a mixture of DNA plasmid vectors: pSIV239.dpol, SIV239.sgp130, SIV251.sgp130, SIV316.sgp130 and SIV239.sgp110, in a physiologically acceptable carrier, wherein said multiple administrations comprise at least a gene gun administration of one of the DNA plasmid vectors to the skin of the mammal, whereby the SIV infected cells are reduced in the mammal as a result of SIV antigen expression by the administered plasmid vectors; and

(II) A method of reducing HIV infected cells in a mammal, the method comprising administering to said mammal multiple administrations of a mixture of DNA plasmid vectors: pCMV/HIV-1-NL4-3.dpol, pCMV/HIV-1-HXB-2.env, pCMV/HIV-NL4-3env, Jw4303/HIV-1-HXB-2.sgp120, and JW4303/HIV-1-HXB-2.sgp140, in a physiologically acceptable carrier, wherein said multiple administrations comprise at least a gene gun administration of one of said DNA plasmid vectors to the skin of said mammal, whereby the HIV infected cells are reduced in the mammal as a result of HIV antigen expression by the plasmid vectors.

In determining whether Appellants enabled the full scope of the claimed invention each of the following factors were considered; the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation necessary.

**NATURE OF THE INVENTION**

The full scope of the claimed invention encompasses DNA immunization or DNA vaccine therapy of using any DNA encoding any SIV or HIV antigen in any mammal including humans so as to generate a protective response, *e.g.*, partial protection and/or complete protection against an infection of any SIV strain or HIV strain.

**WORKING EXAMPLES AND GUIDANCES**

While the breadth of the presently pending claims encompasses any mammal including humans, the claimed subject matter when read in light of the as-filed specification coupled with the state of the prior art as a whole is focused mainly on prevention of SIV or HIV infection in humans, particularly since it is apparent from the state of the prior art exemplified by Haynes (Science, 260, pp. 1279-1286, 1993) that diseased AIDS symptoms are primarily developed in

humans infected by SIV or HIV viruses. In the specification and in the Declarations of record excluding Paper No. 15, several examples are given in which mice, chickens, and ferrets were immunized with DNA encoding the influenza hemagglutinin types H1 and H7. However, the claimed invention as presently pending is not directed to any influenza DNA vaccine, but rather to only SIV or HIV vaccines.

More specifically as to the guidance and/or evidence provided by the application to demonstrate the enablement of the full breadth of the claimed invention, examples 11 –15 of the specification describe making and administering DNA vectors encoding antigens of SIV and HIV, but Appellants have not provided any guidance and/or factual evidence showing a reasonable extrapolation from the disclosure any DNA vaccine/immunization or protective effect.

The only factual evidence that is most relevant to the claimed invention is the Robinson Declaration (paper NO: 15). The Robinson Declaration teaches that multiple administrations, *e.g.*, gene gun, intramuscular, and intravenous administration, of a mixture of specifically constructed plasmids encoding at least a SIV env antigen (extracellular domain and/or the receptor binding subunit of a SIV envelope protein) to macaques caused viral loads to be reduced to chronic levels more rapidly than occurs in control animals, but neither the application, nor any of the Declaration of record, nor any prior art of record, nor any art of record even five years after the effective filing date of the application shows by factual evidence that **any** administration of **any** SIV or HIV antigen expressing plasmid vector as disclosed by the as-filed specification by

**any** delivery route so as to generate a protective response against SIV and/or HIV can be reasonably reproduced in a representative number of SIV or HIV infectious mammals including humans. Even in the Robinson Declaration (paper No. 15), the macaque model fails to protect the immunized animal against SIV infection or death by AIDS (caused by any HIV strain infection). In fact, the Robinson Declaration is an indicia of a reasonable predictability of the claimed subject matter, *e.g.*, SIV or HIV DNA vaccine. While several references as indicated in the Haynes reference suggest that cellular immune responses, *e.g.*, cytotoxic lymphocyte or CD4+ production, may be essential for the fight against development of AIDS, the Robinson Declaration (Paper No. 15) in fact indicates that "consistent with failure to achieve long-term reductions in viral loads, all of the vaccine animals exhibited steadily declining CD4+ cells", that "the trail was terminated at one year post-challenge", that "at this time, the three macaques in the gene-gun only group, and one of the two control macaques (the one with the steady CD4+ level), had succumbed to AIDS (figure 8), and that "the second control monkey and the four monkeys in the multiple route group did not have clinical signs of AIDS at the time of euthanasia". In addition, the Robinson Declaration (Paper No. 15) indicates that by week 12 that the control group achieved similar reductions in viral loads, and that, more importantly, the CD4+ cells declined in both groups (the Declaration, page 17) and the CD4+ counts were no different from the control group. As a result, the fact that even in Appellants' results obtained with anti-SIV vaccine in macaques, immunized macaques in the gene-gun only group did not exhibit any protective

response against SIV infection but rather died subsequently as the control macaques, does not indicate with any factual evidence a reasonable extrapolation from the disclosure including the SIV mascaque model to a full scope of the claims that encompasses any SIV or HIV DNA vaccine regardless of what SIV antigen expressing plasmids and/or routes of administrations are employed in any mammal including humans.

**STATE OF THE ART AND ANALYSIS OF THE ISSUES**

More specifically as to the lack of a reasonable correlation even between the SIV mascaque model and an SIV infectious animal that is intended for DNA immunization, Haynes teaches on page 1280, first column:

"In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection. In general, current animal models of HIV or simian immunodeficiency virus (SIV) infection either do not develop AIDS symptoms, do not develop immune responses analogous to human anti-HIV T and B cell response, or involve the use of endangered species such as chimpanzees. Thus, many important scientific questions of HIV vaccine development must be answered in human clinical trails". (References omitted).

While it is apparent that neither MPEP guidelines nor the Office actions of record do not require human testing data, the U.S. P.T.O has determined that on the basis of Appellants' disclosure, the state of the prior art, the nature of the invention, the breadth of the claims, the

working examples, which demonstrates the reasonable basis for questioning the assertions regarding the enablement of the claimed invention, the present claims are properly rejected under 35 U.S.C. 112, first paragraph, particularly since the totality of the prior art references does provide doubt as to the enablement of the broad scope of SIV DNA vaccines as claimed, let alone claimed HIV DNA vaccines, particularly since an unpredictability of a particular art area alone, *e.g.*, SIV vaccines for use in any infectious mammal, provides a reasonable doubt as to the accuracy of the broad statement made and/or the mascaque model of using multiple routes of administrations of specifically constructed plasmid vectors in support of enablement of the subject matter being sought in the claims.

Not only the mascaque model does not represent a reasonable of the full breadth of claims directed to SIV vaccines for use to generate any protective response in any SIV infectious mammal including humans, the state of the art of DNA vaccine remains unpredictable at the time the invention was made. For example, Tang *et al.* (Nature, Vol. 356, Vol. 356, pp. 152-154, 1992) indicate that while gene gun administrations of an antigen expressing plasmids into the skin of mice generate antibody responses, "injection of the hGH plasmid (50 ug) into the skin of two mice with a hypodermic needle did not produce a response", and that "Biolistic inoculations into the liver produce hGH but did not elicit an immune reaction (eight mice tested)" (page 154, column 1, last paragraph).

Furthermore, as indicated on page 4 of the office action dated 8/25/1997, it was well-

known at the time the invention was made that it is impossible to predict whether an untested antigen of an infectious pathogen in the form of a DNA vaccine, will elicit a protective immune response in a given type of animal.

As a result, even if data were provided showing that multiple administrations comprising at least a gene-gun administration of specifically constructed plasmid vectors encoding inactivated SIV (pol deleted SIV vectors) and plasmid vectors expressing at least an SIV *env* antigen elicit a reduction of SIV load in mascaques, there is no evidence in the as-filed specification or in the prior art of record that would convince a skilled artisan that such result is reasonably predictive of any claim directed to any SIV DNA vaccine and/or immunization methods of using any administration route and any SIV antigen expressing vector, let alone claims directed to HIV DNA vaccines and immunization methods of using any HIV DNA vaccine and any administration route in any HIV infectious mammal including humans, which methods must produce a protective response.

More importantly as to the higher unpredictiable nature of the claimed invention directed to HIV vaccines and/or immunization methods of using any HIV DNA vaccine and any administration route in any HIV infectious mammal including humans, Haynes teaches that the immune correlates for protection against HIV are not known, that there is no animal model that mirrors human HIV infection, and that current animal models for HIV infection do not develop AIDS symptoms or anti-HIV immune responses analogous to those of HIV-infected humans, so

that it is impossible to determine whether observation of a given immune response to an immunodeficiency virus vaccine in an animal model indicates that any HIV antigen expressing DNA vaccine plasmid vector would actually confer any protection against HIV infection in any infectious mammal including humans (pages 1280, column 1).

As to the complexity of the immune responses played in generating a protective response against any HIV strain in any infectious mammal including humans, Hoffenbach *et al.* (J. of Immunology, 142, 2, pp. 452-462, 1989) on page 459 indicates that "no clear correlation exists at present between the presence of HIV-specific CTL and resistance to progression toward AIDS." Consequently, it is unpredictable as to whether a simulation of an HIV-specific antibody response as being correlatable to the SIV working models shown in the Robinson Declaration (paper No. 15) would result in any protective immune response against any HIV strain in any infectious mammal including humans. In fact, Butini *et al.* (J. or Cellular Biochemistry, Suppl. 18B: 147, abstract J306, 1994) further confirms the doubts expressed by the prior art of record by indicating that the patient with high HIV-specific CTL activity had rapidly progressive disease, while the patient with no CTL activity was found to have no progression of immunodeficiency disease. Even in 1996, Glasser (Genetic Engineering News, Biotech Firms Shifts Focus Toward Therapeutic HIV vaccine Development, 1996) reviewed the state of the art of DNA HIV vaccine in the past indicates:

"Many obstacles that have thwarted HIV vaccine development in the pas continue to

challenge researchers and clinicians. These obstacles are:

- The need to induce humoral (antibody), cellular (cytotoxic T lymphocyte-mediated), and mucosal (preventing viral entry at mucosal surfaces) immunity.
- HIV resides in immunoprivileged sites and can remain latent for years.
- HIV causes immunosuppression, further hindering the body's ability to contain the virus and prevent opportunistic infections.
- How the virus destroys immune cells is not fully understood.
- No good animal model exists.
- HIV continuously mutates: different strains are prevalent in various parts of the world; field isolates often differ from the laboratory strains used to develop vaccines; and after infection, HIV can mutate within the host, and an infected person can harbor multiple forms of the virus.
- The appropriate clinical end points for evaluating therapeutic vaccines are not clear."

More specifically as to the variability of HIV antigen that are candidates for use in a HIV vaccine, Rekosh *et al.* (PNAS, vol. 85, pp. 334-338, 1988) teach that while at the present time, the envelope glycoprotein (*env*) of HIV (gp160/gp120) must be regarded as the prime candidate for the creation of a subunit vaccine (page 334, column 1, first paragraph), further studies are needed to define the functional regions of binding and fusion within its envelope protein and to demonstrate the link that hopefully exists between these regions and virus neutralization (page

334, column 2).

Even in DNA vaccines done chimps which are known to have very similar immune system to people, Weiss (The Washington Post, Genetic Vaccine Keeps Chimps Protected Against AIDS Virus, page A2, 4/30/1997) summarizes the beliefs of several skilled artisans, indicates:

- "Genetic vaccination is one of several approaches under investigation in what has remained a mostly disappointing effort to develop an AIDS vaccine. Success has been hampered by HIV's great variability, which makes it a moving target for vaccine developers, and by the lack of a good animal model for testing candidate vaccines";
- "Equally frustrating, scientists still don't know what, precisely, an AIDS vaccine ought to do in the body to be effective. Neither of the immune system's two armies for fending off microbial invaders-antibodies and killers T cells- reliably win the battle against HIV. Vaccines seek to boost the strength of one or both of those immune system armies, but no one knows which is more important";
- "Marc Girard, chief of molecular virology at the Pasteur Institute near Paris, was among several who criticized use of the SF2 strain to test AIDS vaccines. 'The challenge they used us not a strong challenge,' he said. 'It 's a wimpy virus and this vaccine may not be strong enough for a more virulent strain".

Even in 1998, Cohen and Fauci (JAMA, Vol. 280, Vol. 280, No. 1: 87-88, 1998) indicate that "the development of a safe and effective vaccine continues to encounter a host of sobering

challenges, including geographic variability of HIV subtypes, and the lack of correlates of protective immunity in HIV infection (page 88, column 1).

More specifically as to the lack of a reasonable correlation between a showing of production of antibodies to a tested HIV antigen expressing plasmid and any protective response as claimed, Kuby (Immunology, W.H. Freeman and Company, New York, 1992) indicates that "Unfortunately the presence of high titers of circulating antibody to HIV proteins in no way indicates protective immunity", that "the antibody has so little effect seems to be frequent antigenic drift in HIV", that "some studies have indicated that anti-HIV antibody-HIV immune complexes to Fc receptors on macrophages and subsequent receptor medicated endocytosis may lead to increased HIV infection of macrophages", and that "several observations indicate that immune regulation is disturbed in AIDS patients, although the mechanisms underlying these disturbances are not entirely clear".

Thus, in view of the lack of any established nexus between the guidance provided by the as-filed specification including the *in vivo* data shown in the SIV working examples and the subject matter being sought in the claims, one must evaluate the evidence presented and determine whether applicant has demonstrated such correlation or a reasonable likelihood of such. In the instant case, the data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility. This conclusion coupled with state of the art, as indicated in the stated Office actions, is consistent with a finding of lack of enablement for the

practice of what is claimed. Appellants' arguments fail to address these art-recognized limitations with regard to the unpredictability of claiming a full breadth encompassing any SIV and/or HIV DNA vaccine for use to generate any protective responses in any infectious mammal including humans at the time the invention was made. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, it is not apparent as to how a skilled artisan, without any undue experimentation, reasonably extrapolates from the Appellant's disclosure including the Mascaque SIV model to the entire breadth of the claims. Note that also Gilboa and Smith (TIG, 1994, pages 141-142, paragraph bridging pages 141-142) indicate that one drawback to using SIV infected macaques is the difference in the biology of SIV and HIV.

Even in the Mascaque model shown in the Robinson Declaration (paper No. 15), though the four monkeys in the multiple route did not have clinical signs of AIDS at the time of euthanasia, neither did not one of the two (50%) of the control monkeys. Furthermore, the trial was terminated at one year post challenge. The time for the AIDS progression can be much longer than one year. The challenge virus was an uncloned SIV mac251 virus. Johnson *et al.* (Intern. Rev. Immunol. Vol. 8, pp. 55-63, 1992) state that it typically takes longer than one year for AIDS progression where the virus is other than a 239 (the explanation for Table 1 appearing on page 58). Therefore it is not apparent that the Mascaque models using multiple administrations comprising at least a gene gun administration had any level of protection for

disease manifestation.

*(12) New Ground(s) of rejection*

This examiner's answer does not contain any new ground of rejection.

*(13) Response to Argument*

The commentary (pages 4-11) in the Appeal Brief has been noted and considered. It is not persuasive for the reasons set forth above and for the following reasons:

Appellant assert (page 4, last paragraph) that the Patent Office does not provide a reason to doubt the objective truth of the statements contained in the as-filed specification, *e.g., In re Marzocchi,* the comments are not found persuasive because the previously and above stated rejections are indicative of unpredictability which leads to doubt of the objective statements in the present application and therefore to the rejection under 35 U.S.C. § 112, first paragraph.

In response to Appellant's assertion (the brief, page 5) that the specification, *e.g.,* Examples 11-15, page 45 through page 49, describes a number of constructs (plasmid vectors expressing SIV *env* antigens or HIV *env* antigens) for use in the claimed invention, *e.g.,* vaccine or immunization against any infectious mammal including humans, that one skilled in the art would understand that constructs other than these specific constructs could also be used in the methods of the invention, and would be able to assess the efficacy of such constructs, that one of ordinary skill in the art would be able to make these particular constructs without undue

experimentation, and that there is nothing of record which might suggest that the guidance provided in the Specification would be insufficient to enable the skilled artisan to practice these claims, the comments are not found persuasive because:

- Section 112, Paragraph 1, provides, in relevant part that "[t]he specification shall contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. . . ." The issue at hand is not whether or not any plasmid vector expressing any SIV or HIV antigen can be made by simple and routine DNA recombinant techniques, but rather whether one skilled in the art would have been able to have employed the constructed plasmid vectors as DNA vaccines for the intended use of generating any protective responses in any infectious mammals including humans, without any undue experimentation, particularly on the basis of Appellant's disclosure and the doubts expressed by the art of record;
- For the claimed invention to be enabling under 35 U.S.C. 112, first paragraph, the specification of the as filed application must teach one skilled in the art how to make and use the full scope of the claimed invention "without undue experimentation", and the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to one skilled in the art. However, the state of the art

exemplified by Haynes, Tang *et al.*, Kuby, Rekosh *et al.*, Cohen and Fauci, Gilboa and Smith, Huylebroeck *et al.*, Glasser and Butini indicates that determination as to which of SIV or HIV antigen expressing DNA construct is effective for use as a DNA vaccine against any infection of any SIV or HIV strain, respectively, in any infectious mammal is not reasonably predictable;

Furthermore, determining an effective route of DNA administration other than gene gun administration through the skin of an animal, and transferring the delivered DNA construct getting appropriate and specific activation of immune responses in an amount sufficient and effective to produce any infectious mammals including human remains unpredictable at the time the invention was made (see Tang *et al.*, Haynes for example). In addition, Kuby, for example, teaches that the presence of high titers of circulating antibody to HIV proteins in no way indicates protective immunity.

As a result, as summarized in the art of record, the obstacles of SIV or HIV DNA vaccines even years after the effective filing date of the as-filed specification remains as follows:

- Even in the Mascaque model shown in the Robinson Declaration (paper No. 15), though the four monkeys in the multiple route did not have clinical signs of AIDS at the time of euthanasia, neither did not one of the two (50%) of the control monkeys. Furthermore, the trial was terminated at one year post challenge. The time for the AIDS progression can be much longer than one year. The challenge virus was an

uncloned SIV mac251 virus. Johnson *et al.*, Intern. Rev. Immunol. Vol. 8, pp. 55-63, 1992, state that it typically takes longer than one year for AIDS progression where the virus is other than a 239 (the explanation for Table 1 appearing on page 58). Therefor, it is not apparent that the Mascaque models using multiple administrations comprising at least a gene gun administration had any level of protection for disease manifestation;

- The need to induce humoral (antibody), cellular (cytotoxic T lymphocyte-mediated), and mucosal (preventing viral entry at mucosal surfaces) immunity.
- HIV resides in immunoprivileged sites and can remain latent for years.
- HIV causes immunosuppression, further hindering the body's ability to contain the virus and prevent opportunistic infections.
- How the virus destroys immune cells is not fully understood.
- No good animal model exists.
- HIV continuously mutates: different strains are prevalent in various parts of the world; field isolates often differ from the laboratory strains used to develop vaccines; and after infection, HIV can mutate within the host, and an infected person can harbor multiple forms of the virus.
- The appropriate clinical end points for evaluating therapeutic vaccines are not clear."

In view of the lack of any established nexus between a simple reduction of viral load in

immunized Mascaques wherein multiple administrations comprising at least a gene-gun administration of a specifically named construct, *e.g.*, SIV *env* expressing plasmid vector and the subject matter being sought in the claims, *e.g.*, any protective responses in any infectious mammal including humans against any SIV or HIV strain, one must evaluate the evidence presented and determine whether appellant has demonstrated such correlation or a reasonable likelihood of such. In the instant case, the data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility. This conclusion coupled with state of the art is consistent with a finding of lack of enablement for the practice of what is claimed. Appellant's arguments and application as filed fail to address the art recognized limitations as indicated in the stated rejection for the claimed invention to be enabling on the basis of appellant's disclosure under 35 U.S.C. 112, first paragraph. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, the present claims are properly rejected under 35 U.S.C. 112, first paragraph.

In response to Appellant's assertion (the brief, page 6) that the specification describes a wide variety of routes that are suitable for DNA vaccination in the methods of the invention (page 9), that Example 4 (page 22) where immunization by intramuscular, intravenous, and a combination of routes (intramuscular, intravenous and intraperitoneal) provided excellent protection after challenge with disease, that gene-gun delivered DNA to the epidermis provided

excellent protection after challenge with disease, the comments are not found persuasive because neither example 4 nor example 6 as described in the as-filed specification provides any guidance and/or evidence to the claimed invention directed specifically to any SIV or HIV vaccine. A showing of a protective response against infection by influenza virus in chickens, mice and ferrets is not the same as a claimed invention of any SIV or HIV DNA vaccine which has nothing to do with protection of an influenza infection or influenza DNA vaccine. Due to the acknowledged complex and unpredictable nature of the claimed subject matter, the differences in anatomy, cell biology, genetics, and immunology between different types of animals and between the animal models and infectious mammals that actually develop AIDS symptoms as a result of an infection by a non-lab SIV or HIV strain, the transient gene expressing by routes of administration other than gene-gun administration to the epidermis *in vivo*, the lack of working examples which are reasonably extrapolated to the claimed immunization methods and/or DNA vaccine compositions, *e.g.*, plasmid vector claims, one skilled in the art would recognize that neither the influenza models nor the mascaque models are reasonably predictive of outcome or efficacy in application of SIV or HIV DNA vaccines in any infectious mammals including humans against any naturally infectious SIV or HIV strain.

In response to Appellant's assertion (the brief, page 6, last paragraph, and page 6 bridging page 7) that the outstanding rejection is inapplicable to the composition claims, that given the guidance provided by the specification, one skilled in the art would be able to make and use these

particular constructs without any undue experimentation, the comments are not found persuasive because as indicated in this examiner's answer, the Office has determined based on the entire prosecution history, the nature of the invention, the state of the prior art, the working examples, the levels of a skilled artisan, the as-filed specification including the Robinson Declaration (paper No. 15) does provide a reasonable enablement for claims directed to

- A method of reducing SIV infected cells in a mammal, the method comprising administering to said mammal multiple administrations of a mixture of DNA plasmid vectors: pSIV239.dpol, SIV239.sgp130, SIV251.sgp130, SIV316.sgp130 and SIV239.sgp110, in a physiologically acceptable carrier, wherein said multiple administrations comprises at least a gene gun administration of the DNA plasmid vectors to the skin of the mammal, whereby the SIV infected cells are reduced in the mammal as a result SIV antigen expression;

- Plasmid vectors selected from the group consisting of pSIV239.dpol, SIV239.sgp130, SIV251.sgp130, SIV316.sgp130 and SIV239.sgp110.

- A method of reducing HIV infected cells in a mammal, the method comprising administering to said mammal multiple administrations of a mixture of DNA plasmid vectors: pCMV/HIV-1-NL4-3.dpol, pCMV/HIV-1-HXB-2.env, pCMV/HIV-NL4-3env, Jw4303/HIV-1-HXB-2.sgp120, and JW4303/HIV-1-HXB-2.sgp140, in a physiologically acceptable carrier, wherein said multiple administrations comprises at least a gene gun

administration of said DNA plasmid vectors to the skin of said mammal, whereby the HIV infected cells are reduced in the mammal as a result HIV antigen expression; and

- Plasmid vectors selected from the group consisting of pCMV/HIV-1-NL4-3.dpol, pCMV/HIV-1-HXB-2.env, pCMV/HIV-NL4-3env, Jw4303/HIV-1-HXB-2.sgp120, and JW4303/HIV-1-HXB-2.sgp140.

However, due to the complexity and unpredictable nature of the invention, the variability of antigen expressing SIV or HIV plasmid vectors in producing an intended DNA vaccine effect as contemplated by the specification, the doubts expressed in the art of record, it is not apparent as to how one skilled in the art reasonably extrapolates, without any undue experimentation, from the applicant's disclosure including the claimed composition and plasmid claims to the entire breadth of the claimed invention as claimed.

In response to Appellant's assertion (the brief, pages 7 and 8) that in the case of highly virulent uncloned SIVmac251 rhesus macaque model, partial protection, rather than complete protection, is usually expected, that the model is reasonably extrapolated to the entire breadth of the claimed invention including a full protection against any infection by any SIV or HIV strain in any infectious mammal including humans, the comments are not persuasive because:

- The uncloned SIVmac251 rhesus macaque model does not indicate with any factual evidence that any protective response has been achieved. In fact, in the Mascaque model shown in the Robinson Declaration (paper No. 15), though the four monkeys in

the multiple route did not have clinical signs of AIDS at the time of euthanasia, neither did not one of the two (50%) of the control monkeys. Furthermore, the trial was terminated at one year post challenge. The time for the AIDS progression can be much longer than one year. The challenge virus was an uncloned SIV mac251 virus. Johnson *et al.*, Intern. Rev. Immunol. Vol. 8, pp. 55-63, 1992, state that it typically takes longer than one year for AIDS progression where the virus is other than a 239 (the explanation for Table 1 appearing on page 58). Therefore, it is not apparent that the Mascaque models using multiple administrations comprising at least a gene gun administration had any level of protection for disease manifestation;

- None of the presently pending claims even recites any partial protective response against an SIV infection in an immunized mammal, wherein multiple administrations comprising a gene-gun administration of specifically named constructs were employed, let alone claiming any DNA HIV vaccine against an infection of any HIV strain in any infectious mammal including humans;
- A showing of the use of the "multiple administrations" comprising the gene gun administration through the skin of a mascaque is the same as claiming any administration routes for delivering any DNA vaccine in any mammal including humans, particularly since Tang *et al.* (Nature, Vol. 356, Vol. 356, pp. 152-154, 1992) indicate that while gene gun administrations of an antigen expressing plasmids into the

skin of mice generate antibody responses, "injection of the hGH plasmid (50 ug) into the skin of two mice with a hypodermic needle did not produce a response", and that "Biolistic inoculations into the liver produce hGH but did not elicit an immune reaction (eight mice tested)" (page 154, column 1, last paragraph); and

- Even in 1998, Cohen and Fauci, JAMA, Vol. 280, Vol. 280, No. 1: 87-88, 1998, indicates that "the development of a safe and effective vaccine continues to encounter a host of sobering challenges, including geographic variability of HIV subtypes, and the lack of correlates of protective immunity in HIV infection (page 88, column 1).

More specifically as to the lack of a reasonable correlation between a showing of production of antibodies to a tested HIV antigen expressing plasmid and any protective response as claimed, Kuby, Immunology, W.H. Freeman and Company, New York, 1992, indicates that: "Unfortunately the presence of high titers of circulating antibody to HIV proteins in no way indicates protective immunity", that "the antibody has so little effect seems to be frequent antigenic drift in HIV", that "some studies have indicated that anti-HIV antibody-HIV immune complexes to Fc receptors on macrophages and subsequent receptor medicated endocytosis may lead to increased HIV infection of macrophages", and that "several observations indicate that immune regulation is disturbed in AIDS patients, although the mechanisms underlying these disturbances are not entirely clear".

Thus, in view of the lack of any established nexus between the guidance provided by the

as-filed specification including the *in vivo* data shown in the SIV working examples and the subject matter being sought in the claims, one must evaluate the evidence presented and determine whether Appellants have demonstrated such correlation or a reasonable likelihood of such. In the instant case, the data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility. This conclusion coupled with state of the art, as indicated in the stated Office actions, is consistent with a finding of lack of enablement for the practice of what is claimed. Appellants' arguments fail to address these art-recognized limitations with regard to the unpredictability of claiming a full breadth encompassing any SIV and/or HIV DNA vaccine for use to generate any protective responses in any infectious mammal including humans at the time the invention was made.

In response to Appellant's assertion (the brief, pages 8 and 9) that Appellants disagree with the Examiner's position that a method of reducing viral load would raise issues under 35 U.S.C. 101 as lacking a substantial utility, the comments have been considered and are found persuasive. As a result, the total rejection under 35 U.S.C. 112 first paragraph has been modified to a scope rejection under 35 U.S.C. 112, first paragraph. In fact, the US PTO had called Appellants prior to the writing of this examiner's answer to propose the subject matter limited to reduction of viral loads wherein the materials and method steps are employed as shown in the Robinson Declaration (Paper No. 15), however, Appellants did not accept the proposed amendment.

In response to Appellant's assertion (the brief, pages 9-11) that Gardner and McClure teach that SIV infection in macaques is useful for studying vaccine development in fight against AIDS, that one skilled in the art, given the specification and the state of the art at the time the application was filed, as demonstrated by these references previously cited by Appellants, would find the macaque (SIV) model described in the specification and used in the Declaration (Robinson Declaration) to be an appropriate model that would be predictive for HIV vaccination, the comments are not found persuasive because none of the art cited by Appellants indicates *per se* that a reduction of viral load in the Mascaque model is indicative of a successful SIV DNA vaccine or a reasonable extrapolation to any HIV DNA vaccine as claimed. An indication of the use of a mascaque model as being useful for studying vaccine development is not the same as claiming that a reduction of viral loads in a Mascaque by using multiple administrations of specifically named constructs is the same as a protective effect against the uncloned SIV mac251 infection, let alone protections against any other SIV strain or any HIV strain.

In fact, Gilboa and Smith, TIG, 1994, pages 141-142, paragraph bridging pages 141-142) indicate that one drawback to using SIV infected macaques is the difference in the biology of SIV and HIV.

In addition, Weiss, The Washington Post, Genetic Vaccine Keeps Chimps Protected Against AIDS Virus, page A2, 4/30/1997, summarizes the beliefs of several skilled artisans, indicates:

- "Genetic vaccination is one of several approaches under investigation in what has remained a mostly disappointing effort to develop an AIDS vaccine. Success has been hampered by HIV's great variability, which makes it a moving target for vaccine developers, and by the lack of a good animal model for testing candidate vaccines";
- "Equally frustrating, scientists still don't know what, precisely, an AIDS vaccine ought to do in the body to be effective. Neither of the immune system's two armies for fending off microbial invaders-antibodies and killers T cells- reliably win the battle against HIV. Vaccines seek to boost the strength of one or both of those immune system armies, but no one knows which is more important";
- "Marc Girard, chief of molecular virology at the Pasteur Institute near Paris, was among several who criticized use of the SF2 strain to test AIDS vaccines. 'The challenge they used us not a strong challenge,' he said. 'It 's a wimpy virus and this vaccine may not be strong enough for a more virulent strain".

Even in 1998, Cohen and Fauci, JAMA, Vol. 280, Vol. 280, No. 1: 87-88, 1998, indicates that "the development of a safe and effective vaccine continues to encounter a host of sobering challenges, including geographic variability of HIV subtypes, and the lack of correlates of protective immunity in HIV infection (page 88, column 1).

More specifically as to the lack of a reasonable correlation between a showing of production of antibodies to a tested HIV antigen expressing plasmid and any protective response

as claimed, Kuby, Immunology, W.H. Freeman and Company, New York, 1992, indicates that "Unfortunately the presence of high titers of circulating antibody to HIV proteins in no way indicates protective immunity", that "the antibody has so little effect seems to be frequent antigenic drift in HIV", that "some studies have indicated that anti-HIV antibody-HIV immune complexes to Fc receptors on macrophages and subsequent receptor medicated endocytosis may lead to increased HIV infection of macrophages", and that "several observations indicate that immune regulation is disturbed in AIDS patients, although the mechanisms underlying these disturbances are not entirely clear".

In view of the foregoing, it is readily apparent that the present fact pattern is clearly distinguished from that of the Appellant's assertions and expressed opinions (the brief, pages 10-11). Moreover, the present claims and the claimed subject matter encompass an enormous number of SIV DNA vaccines and HIV DNA vaccines, none of which is reasonably enabling in view of the reasons set forth in the art of record. Furthermore, since reduction of viral loads of SIV is not deemed sufficient to establish any protective response even against the uncloned SIVmac251 strain, and since the Robinson Declaration (Paper No. 15) clearly shows that by week 12 that the control group achieved similar reductions in viral loads, and that, more importantly, the CD4+ cells declined in both groups (the Declaration, page 17) and the CD4+ counts were no different from the control group, one skilled in the art would need to rely on the specification to obtain guidance in the SIV DNA and HIV DNA vaccine as claimed that must produce a

protective response, *e.g.*, partial and/or complete protection, in any infectious mammal including humans against any SIV or HIV strain. The application neither teaches nor provides such guidance. Without such guidance, it is apparent to a skilled artisan that based on the complexity of the nature of the claimed invention and the reasons set forth by the totality of the art of record, the present application does not present any reasonable extrapolation to the subject matter, *e.g.*, of that vaccine effect, being sought in the pending claims, particularly since Appellants arguments do not factually establish such correlation on the basis of appellants disclosure.

Consequently, the application is not enabling in view of the complex and unpredictable nature of the claimed subject matter, *e.g.*, any SIV DNA, any HIV DNA vaccine regardless of what SIV or HIV antigens and/or vector DNA are employed, the molecular biology and variability among SIV and/or HIV strains, the unpredictability of routes of administrations other than a gene gun delivery of a DNA through the skin *in vivo*, the unpredictability of HIV DNA vaccine as expressed in the art of record, the lack of an animal model to show a correlation to a claim of any DNA vaccine for use in any infectious mammal including humans against any SIV or HIV strain, 44, each of which lead to undue experimentation as a requisite for practicing the claimed invention under 35 U.S.C. 112, first paragraph.

Thus, it is readily apparent that the as filed application fails to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that

must supply the novel aspects of an invention in order to constitute adequate enablement, *e.g.*, see *Genetech Inc. V. Novo Nordisk* A/S/, CA FC, 3/13/97, p. 1005).

***(14) Period response to new ground of rejection***

This examiner's answer does not contain any new ground of rejection.

***(15) Oral Argument***

It is noted that a request for oral hearing was filed on March 12, 2001 .

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

DEBORAH J. R. CLARK conferee
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

DAVE T. NGUYEN
PRIMARY EXAMINER

DTN
June 4, 2001

KAREN M. HAUDA, Conferee
KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Patricia Granahan
Hamilton, Brook, Smith & Reynolds
Two Militia Drive
Lexington MA 02173